The listing of claims will replace all prior versions, and listings, of claims in the application:
Listing of Claims:

1. (Original) A proteinaceous particle displaying on its surface a T-cell receptor (TCR), characterised in that

(i) the proteinaceous particle is a ribosome and the TCR is a single chain TCR (scTCR) polypeptide, or dimeric TCR (dTCR) polypeptide pair, or

(ii) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a human scTCR or a human dTCR polypeptide pair, or

(iii) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a non-human dTCR polypeptide pair, or

(iv) the proteinaceous particle is a phage particle, or a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked, and the TCR is a scTCR polypeptide comprising TCR amino acid sequences corresponding to extracellular constant and variable domain sequences present in native TCR chains and a linker sequence, the latter linking a variable domain sequence corresponding to that of one chain of a native TCR to a constant domain sequence corresponding to a constant domain sequence of another native TCR chain, and a disulfide bond which has no equivalent in native T cell receptors links residues of the constant domain sequences.

2. (Original) A proteinaceous particle, displaying on its surface a dimeric T-cell receptor(dTCR) polypeptide pair, or a single chain T-cell receptor (scTCR) polypeptide wherein

the dTCR polypeptide pair is constituted by TCR amino acid sequences corresponding to extracellular constant and variable domain sequences present in native TCR chains, and the scTCR is constituted by TCR amino acid sequences corresponding to extracellular constant and variable domain sequences present in native TCR chains and a linker sequence, the latter linking a variable domain sequence corresponding to that of one chain of a native TCR to a constant domain sequence corresponding to a constant domain sequence of another native TCR chain;

wherein the variable domain sequences of the dTCR polypeptide pair or scTCR polypeptide are mutually orientated substantially as in native TCRs, and

in the case of the scTCR polypeptide a disulfide bond which has no equivalent in native T cell receptors links residues of the polypeptide.

3. (Currently Amended) A proteinaceous particle as claimed in claim 1 ~~or claim 2~~, which is a filamentous phage particle.

4. (Currently Amended) A proteinaceous particle as claimed in claim 1 ~~or claim 2~~, which is a cell with cell surface protein or polypeptide molecules to which the TCR is covalently linked.

5. (Currently Amended) A proteinaceous particle as claimed in claim 1 ~~or claim 2~~, which is a ribosome.

6. (Currently Amended) A proteinaceous particle as claimed in ~~any of the preceding claims~~ claim 1 wherein the C-terminus of one member of the dTCR polypeptide pair, or the C-terminus of the scTCR polypeptide, is linked by a peptide bond to a surface exposed residue

of the proteinaceous particle.

7. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 4~~ claim 1 wherein the C- terminus of one member of the dTCR polypeptide pair, or the C-tenninus of the scTCR polypeptide, is linked by a disulfide bond to a surface exposed cysteine residue of the proteinaceous particle.

8. (Currently Amended) A proteinaceous particle as claimed in ~~any of the preceding claims~~ claim 1 wherein

scTCR polypeptide is displayed which comprises a first segment constituted by an amino acid sequence corresponding to a TCR α or δ chain variable domain

a second segment constituted by an amino acid sequence corresponding to a TCR β or γ chain variable domain sequence fused to the N terminus of an amino acid sequence corresponding to a TCR β chain constant domain extracellular sequence, and

a linker sequence linking the C terminus of the first segment to the N terminus of the second segment,

PROVIDED THAT where the proteinaceous particle is a phage, the scTCR corresponds to a human TCR.

9. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 7~~ claim 1 wherein

a scTCR polypeptide is displayed which comprises a first segment constituted by an amino acid sequence corresponding to a TCR β or γ chain variable domain

a second segment constituted by an amino acid sequence corresponding to a TCR α or

δ chain variable domain sequence fused to the N terminus of an amino acid sequence corresponding to a TCR α chain constant domain extracellular sequence, and

a linker sequence linking the C terminus of the first segment to the N terminus of the second segment

PROVIDED THAT where the proteinaceous particle is a filamentous phage, the scTCR corresponds to a human TCR.

10. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 7~~ claim 1 wherein a scTCR polypeptide is displayed which has

a first segment constituted by an amino acid sequence corresponding to a TCR α or δ chain variable domain sequence fused to the N terminus of an amino acid sequence corresponding to a TCR α chain constant domain extracellular sequence,

a second segment constituted by an amino acid sequence corresponding to a TCR β or γ chain variable domain fused to the N terminus of an amino acid sequence corresponding to TCR β chain constant domain extracellular sequence,

a linker sequence linking the C terminus of the first segment to the N terminus of the second segment, or vice versa, and

a disulfide bond between the first and second chains, said disulfide bond being one which has no equivalent in native αβ or βδ T cell receptors,

the length of the linker sequence and the position of the disulfide bond being such that the variable domain sequences of the first and second segments are mutually orientated substantially as in native αβ or βδ T cell receptors.

11. (Original) A proteinaceous particle as claimed in claim 10 wherein the linker sequence

has the formula -P-AA-P- wherein P is proline and AA represents an amino acid sequence wherein the amino acids are glycine and serine.

12. (Currently Amended) A proteinaceous particle as claimed in claim 10 ~~or claim 11~~ wherein the linker sequence links the C terminus of the first segment to the N terminus of the second segment.

13. (Original) A proteinaceous particle as claimed in claim 12 wherein the linker sequence consists of from 26 to 41 amino acids.

14. (Original) A proteinaceous particle as claimed in claim 13 wherein the linker sequence consists of 29,30, 31 or 32 amino acids.

15. (Original) A proteinaceous particle as claimed in claim 13 wherein the linker sequence consists of 33,34, 35 or 36 amino acids.

16. (Original) A proteinaceous particle as claimed in claim 13 wherein the linker sequence has the formula-PGGG- $(SGGGG)_5$-P- wherein P is proline, G is glycine and S is serine.

17. (Original) A proteinaceous particle as claimed in claim 13 wherein the linker sequence has the formula-PGGG-$(SGGGG)_6$-P- wherein P is proline, G is glycine and S is serine.

18. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 7~~ claim 1 wherein a dTCR polypeptide pair is displayed which is constituted by

a first polypeptide wherein a sequence corresponding to a TCR α or δ chain variable domain sequence is fused to the N terminus of a sequence corresponding to a TCR α chain constant domain extracellular sequence, and

a second polypeptide wherein a sequence corresponding to a TCR β or γ chain variable domain sequence fused to the N terminus a sequence corresponding to a TCR β chain constant domain extracellular sequence,

the first and second polypeptides being linked by a disulfide bond which has no equivalent in native αβ or γδ T cell receptors.

19. (Currently Amended) A proteinaceous particle as claimed in ~~any preceding~~ claim 1 wherein the displayed dTCR polypeptide pair or scTCR polypeptide have amino acid sequences corresponding to αβ TCR extracellular constant and variable domain sequences.

20. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 19~~ claim 1 wherein the displayed dTCR polypeptide pair or scTCR polypeptide have amino acid sequences corresponding to extracellular αβ TCR constant domain sequences and γδ TCR variable domain sequences.

21. (Currently Amended) A proteinaceous particle as claimed in ~~any preceding~~ claim 1 wherein the displayed dTCR polypeptide pair or scTCR polypeptide have amino acid sequences corresponding to non-human extracellular ap TCR constant domain sequences and human TCR variable domain sequences.

22. (Currently Amended) A proteinaceous particle as claimed in ~~any of the preceding claims~~

claim 1 wherein an amino acid sequence of one member of the displayed dTCR polypeptide pair, or an amino acid sequence of the displayed scTCR, corresponds to a native TCR extracellular constant chain Ig domain sequence.

23. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 1 to 22~~ claim 1 wherein the displayed dTCR polypeptide pair or displayed scTCR, includes sequences corresponding to native TCR extracellular constant chain Ig domain sequences.

24. (Original) A proteinaceous particle as claimed in claim 23 wherein a disulfide bond links amino acid residues of the said constant chain Ig domain sequences, which disulfide bond has no equivalent in native TCRs.

25. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues corresponding to amino acid residues whose (3 carbon atoms are less than 0.6 nm apart in native TCRs.

26. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues substituted for Thr 48 of exon 1of TRAC*01 and Ser 57 of exon 1 of TRBC1*01 orTRBC2*01 or the non-human equivalent thereof.

27. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues substituted for Thr 45 of exon 1of TRAC*01 and Ser 77 of exon 1 of TRBC1*01 orTRBC2*01 or the non-human equivalent thereof.

28. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues substituted for Tyr 10 of exon 1 of TRAC*01 and Ser 17 of exon 1 of TRBC1*01 or TRBC2*01 or the non-human equivalent thereof.

29. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues substituted for Thr 45 of exon 1 of TRAC*01 and Asp 59 of exon 1 of TRBC1*01 or TRBC2*01 or the non-human equivalent thereof.

30. (Original) A proteinaceous particle as claimed in claim 24 wherein the said disulfide bond is between cysteine residues substituted for Ser 15 of exon 1 of TRAC*01 and Glu 15 of exon 1 of TRBC1*01 or TRBC2*01 or the non-human equivalent thereof.

31. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 23 to 30~~ claim 23 wherein the sequences corresponding to native TCR extracellular constant chain Ig domain sequences are truncated at their C-termini relative to said native sequences such that the cysteine residues which form the native interchain disulphide bond are excluded.

32. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 23 to 30~~ claim 23 wherein in the sequences corresponding to native TCR extracellular constant chain Ig domain sequences the cysteine residues which form the native interchain disulphide bond are substituted by non-cysteine residues.

33. (Original) A proteinaceous particle as claimed in claim 32 wherein the cysteine residues which form the native interchain disulfide bond are substituted by serine or alanine.

34. (Currently Amended) A proteinaceous particle as claimed in ~~any of the preceding claims~~ claim 1 wherein in the displayed dTCR or scTCR there is no unpaired cysteine residue corresponding an unpaired cysteine residue present in a native TCR.

35. (Currently Amended) A proteinaceous particle as claimed in ~~any of claims 23 to 34~~ claim 23 wherein the sequences corresponding to native TCR extracellular constant chain Ig domain sequences are truncated N-terminal to residues corresponding to those which form the non-native interchain disulphide bond.

36. (Original) A proteinaceous particle as claimed in claim 1 which is a filamentous phage particle displaying on its surface a dimeric T-cell receptor(dTCR) polypeptide pair, the said pair being constituted by

a first polypeptide wherein a sequence corresponding to a TCR α chain variable domain sequence is fused to the N terminus of a sequence corresponding to a TCR α chain constant domain extracellular sequence, and

a second polypeptide wherein a sequence corresponding to a TCR β chain variable domain sequence is fused to the N terminus a sequence corresponding to a TCR β chain constant domain extracellular sequence,

the first and second polypeptides being linked by a disulfide bond between cysteine residues substituted for Thr 48 of exon 1 of TRAC*01 and Ser 57 of exon 1 ofTRBC1 *01 orTRBC2*01 or the non-human equivalent thereof,

the C-terminus of one member of the dTCR polypeptide pair being linked by a peptide bond to a coat protein of the phage.

37. (Currently Amended) A diverse library of dTCR polypeptide pairs or scTCR polypeptides displayed on proteinaceous particles said dTCR polypeptide pairs or scTCR polypeptides having the structural features defined in ~~any of claims 8 to 36~~claim 8.

38. (Original) A diverse library as claimed in claim 37 wherein the diversity resides in the variable domain (s) of the dTCR or scTCR polypeptides.

39. (Currently Amended) A diverse library as claimed in ~~any of claims 37 to 39~~ claim 37 wherein the proteinaceous particles are filamentous phage particles.

40. (Original) A diverse library of filamentous phage particles as claimed in claim 35, wherein the diversity resides in one or more of the complementarity determining regions of the variable domain (s) of the dTCR or scTCR polypeptides and/or in one or more of the framework regions of the complementarity determining regions of the displayed dTCR or scTCR polypeptides.

41. (Currently Amended) Nucleic acid encoding (a) one chain of a dTCR polypeptide pair and (b) the other chain of a dTCR polypeptide pair fused to a nucleic acid sequence encoding a protein capable of forming part of the surface of a proteinaceous particle; or nucleic acid encoding a scTCR polypeptide fused to a nucleic acid sequence encoding a protein capable of forming part of the surface of a proteinaceous particle, the dTCR pair or scTCR having the structural features defined in ~~any of claims 8 to 36~~claim 8.

42. (Currently Amended) An expression vector comprising a nucleic acid as claimed in claim 41, or a composition comprising a first vector comprising nucleic acid (a) as defined in claim ~~42~~41 and a second vector comprising nucleic acid (b) as defined in claim ~~42~~41.

43. (Original) An expression system comprising phagemid or phage genome vectors expressing nucleic acid as claimed in claim 41.

44. (Original) An expression system as claimed in claim 43 wherein the phagemid or phage genome vectors is (are) derived from a filamentous phage

45. (Original) An expression system as claimed in claim 44 wherein the phagemid or phage genome vectors encode (s) bacteriophagegill orgVIII coat proteins.

46. (Currently Amended) An expression system as claimed in ~~any of claims 43 to 45~~ claim 43 where a vector contains a sequence or sequences which limit constitutively or inducibly the amount of TCR polypeptide expressed by the vector to a desired level.

47. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) is (are) weak promoter sequence (s)

48. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) is (are) mutated ribosome binding site (s).

49. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) is

(are) miss-sense suppressor stop codon (s).

50. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) is (are) mutated start codon (s).

51. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) is (are) promoter sequence (s) amenable to metabolite-mediated modification of promoter strength.

52. (Original) An expression system as claimed in claim 46 wherein the said sequence (s) contain (s) a number of codons less preferred by the expression system being utilised.

53. (Currently Amended) A host cell comprising nucleic acid as claimed in claim 41~~, an expression vector as claimed in claim 42 or an expression system as claimed in any of claims 43 to 52~~.

54. (Currently Amended) A host cell harbouring a phagemid expression system as claimed in ~~any of claims 43 to 52~~claim 43, and a helper phage.

55. (Currently Amended) A method for the identification of TCRs with a specific characteristic, said method comprising subjecting a diverse library of TCRs displayed on proteinaceous particles as claimed in ~~any of claims 37 to 40~~ claim 37 to

a selection process which selects for said characteristic, and isolating proteinaceous particles which display a TCR having said characteristic, and optionally to an amplification

process to multiply the isolated particles

and/or

a screening process which measures said characteristic, identifying those proteinaceous particles which display a TCR with the desired characteristic and isolating these proteinaceous particles, and optionally to an amplification process to multiply the isolated particles.

56. (Original) A method as claimed in claim 57 wherein the specific characteristic is increased affinity for a TCR ligand.

57. (Currently Amended) A method for detecting TCR ligand complexes, which comprises:

(i) providing a TCR-displaying proteinaceous particle (s) as claimed in ~~any of claims 1 to 41~~claim 1;

(ii) contacting said TCR-displaying proteinaceous particle (s) with a putative ligand complex; and

(iii) detecting binding of the said TCR-displaying proteinaceous particle (s) to the putative ligand complexes.

58. (Original) A method as claimed in claim 57 wherein the putative TCR ligand complexes are peptide-MHC complexes.

59. (Currently Amended) A method of identifying an inhibitor of the interaction between a TCR- displaying proteinaceous particle (s) as claimed in ~~any one of claims 1 to 41~~claim 1, and a TCR-binding ligand comprising contacting the TCR-displaying proteinaceous particle

with a TCR-binding ligand, in the presence of and in the absence of a test compound, and determining whether the presence of the test compound reduces binding of the TCR-displaying proteinaceous particle (s) to the TCR-binding ligand, such reduction being taken as identifying an inhibitor.

60. (Currently Amended) TCR specific for a given TCR ligand, which (i) has the structural features defined in ~~any of claims 8 to 36~~claim 8, (ii) is mutated in the variable domain (s) relative to the native TCR specific for said TCR ligand and which (iii) has a Kd for the said TCR ligand less than that of the native TCR.

61. (Currently Amended) A TCR specific for a given TCR ligand, which (i) has the structural features defined in ~~any of claims 8 to 36~~claim 8, (ii) is mutated in the variable domain (s) relative to the native TCR specific for said TCR ligand and which (iii) has a Kd for the said TCR ligand less than that of the native TCR as measured by Surface Plasmon Resonance.

62. (Currently Amended) A TCR specific for a given TCR ligand, which (i) has the structural features defined in ~~any of claims 8 to 36~~claim 8, (ii) is mutated in the variable domain (s) relative to the native TCR specific for said TCR ligand and which (iii) has anoff-rate (koff) for the said TCR ligand less than that of the native TCR

63. (Currently Amended) A TCR specific for a given TCR ligand, which (i) has the structural features defined in ~~any of claims 8 to 36~~claim 8, (ii) is mutated in the variable domain (s) relative to the native TCR specific for said TCR ligand and which (iii) has an off-rate ($k_{off}$) for the said TCR ligand less than that of the native TCR as measured by Surface

Plasmon Resonance.

64. (Currently Amended) A dimeric TCR as claimed in ~~any of claims 60 to 63~~ claim 60 which has the structural features of an αβ heterodimeric TCR ~~defined in any of claims 18 to 36~~ constituted by

a first polypeptide wherein a sequence corresponding to a TCR α chain variable domain sequence is fused to the N terminus of a sequence corresponding to a TCR α chain constant domain extracellular sequence, and

a second polypeptide wherein a sequence corresponding to a TCR β chain variable domain sequence fused to the N terminus a sequence corresponding to a TCR β chain constant domain extracellular sequence,

the first and second polypeptides being linked by a disulfide bond which has no equivalent in native αβ T cell receptors.

65. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 64~~ claim 60 which is mutated relative to the native TCR in at least one complementarity determining region and/or framework region thereof.

66. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 65~~ claim 60 which is specific for a given MHC type or types.

67. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 65~~ claim 60 which is specific for a given pMHC.

68. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 65 or 67~~ claim 60 which is specific for the HLA-A2 Tax peptide (LLFGYPVYV) (SEQ ID 21) complex.

69. (Original) A TCR as claimed in claim 68 comprising the beta chain variable domain amino acids shown in SEQIDs 172,173, 174, or 175.

70. (Original) A TCR as claimed in claim 68 comprising one of more of beta chain variable domain amino acids 99M, 99V,1005, 100P, 101A, 102E, 102Q, 104H,105P, 105D and 106Q using the numbering shown in SEQ ID 171.

71. (Original) A TCR as claimed in claim 68 comprising beta chain variable domain amino acids 99M,100S and 101A, using the numbering shown in SEQ ID171.

72. (Original) A TCR as claimed in claim 68 comprising beta chain variable domain amino acid 105D, using the numbering shown in SEQ ID 171

73. (Original) A TCR as claimed in claim 68 comprising beta chain variable domain amino acids 99V and 100P, using the numbering shown in SEQ ID 171.

74. (Original) A TCR as claimed in claim 68 comprising beta chain variable domain amino acids 104H and 105P, using the numbering shown in SEQ ID 171.

75. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 65 or 67~~ claim 60 which is specific for the HLA-A2 NY-ESO peptide (SLLMITQC) (SEQ ID 22) complex.

76. (Currently Amended) Nucleic acid encoding a TCR as claimed in ~~any of claims 60 to 78~~claim 60.

77. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 75~~ claim 60 associated with a therapeutic compound.

78. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 75~~ claim 60 associated with an imaging compound.

79. (Currently Amended) A TCR as claimed in ~~any of claims 60 to 75~~ claim 60 associated with a cytotoxic compound.

80. (Currently Amended) A TCR as claimed in ~~claims 77 or 79~~ claim 77 wherein theTCR is specific for the HLA- A2 Tax peptide (LLFGYPVYV) (SEQ ID 21) complex.

81. (Currently Amended) A TCR as claimed in ~~claims 77 or 79~~ claim 77 wherein the TCR is specific for the HLAA2 NY-ESO peptide (SLLMITQC) (SEQ ID 22) complex.

82. (Currently Amended) A method of treatment of HTLV-1 infection comprising administering to a subject suffering such infection an effective amount of a TCR as claimed in ~~any of claims 68 to 74, or claim 79~~ claim 68.

83. (Currently Amended) ~~The use of~~ A composition comprising an effective amount of a

TCR as claimed in ~~any of claims 68 to 74, or claim 79~~ claim 68 ~~in the preparation of a composition~~ for the treatment of HTLV-1 infection.

84. (Currently Amended) A method of treatment of cancer comprising administering to a subject suffering such cancer an effective amount of a TCR as claimed in claim 75 ~~or claim 81~~.

85. (Currently Amended) A composition comprising an effective amount of ~~The use of~~ a TCR as claimed in claim 75 ~~or claim 81 in the preparation of a composition~~ for the treatment of cancer.